Office of Environmental Health Hazard Assessment

Joan E. Denton, Ph.D., Director
Headquarters • 1001 I Street • Sacramento, California 95814
Mailing Address: P.O. Box 4010 • Sacramento, California 95812-4010
Oakland Office • Mailing Address: 1515 Clay Street, 16th Floor • Oakland, California 94612

Agency Secretary

Arnold Schwarzenegger
Governor

M E M OR A N D U M

TO: Gary T. Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

Charles M. Andrews, Chief
Worker Health and Safety Branch
Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, California 95812-4015

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
1515 Clay Street, 16th Floor
Oakland, California 94612

DATE: September 15, 2003

SUBJECT: COMMENTS ON DPR'S DRAFT RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT METHYL PARATHION

In a memorandum dated August 11, you requested our review of a draft risk characterization document (RCD) and a draft exposure document for the pesticide active ingredient, methyl parathion, prepared by the Department of Pesticide Regulation (DPR). You requested that we complete our review by September 15, 2003. We have completed our review of these draft documents for O, O-dimethyl O-(4-nitro-phenyl) phosphorothioate (methyl parathion). We find the documents well prepared and are happy to discuss our comments as provided below. (Also see attachment.)

Methyl parathion is currently registered in California as an insecticide to control insect pests on food and feed crops, including the following 13 commodities: barley, dry beans, corn, cotton, oats, onions, dry peas, pecans, potatoes, rice soybeans, walnuts and wheat. Over 90% of its total use in California is on walnuts. Methyl parathion is one of the oldest and most toxic anticholinesterase insecticides classified as a Category I toxicant and a restricted-use pesticide.

Methyl parathion is also listed under the California Toxic Air Contaminant Identification and Control Act of 1983 (AB1807) as a chemical known to the State of California to be a Toxic Air Contaminant.

Overall, we support the approaches and procedures used for characterizing the health risk of methyl parathion in the draft RCD for methyl parathion. We especially acknowledge the efforts made to substantiate the choices of studies used for risk assessment, predictions and discussions of issues that might be raised by reviewers, and identification of numerous uncertainties pertinent to the risk estimates. While the current version of the draft RCD covers the relevant issues for a risk assessment document, it could benefit from clarifying certain issues.

A summary of our comments on the draft RCD for methyl parathion is presented below. For more details on these comments, please refer to the attachment.

1. We recommend comparing the choices of critical studies, toxicological endpoints and no effect levels (NOELs) made by DPR in its previous risk assessment of methyl parathion (Evaluation of Methyl Parathion as a Toxic Air Contaminant, August 1999) and the current RCD. The toxic air contaminant (TAC) document has received public comment and was reviewed by the Scientific Review Panel on air toxics. Several of the current choices in the RCD are different from those in the TAC document. In this regard, we recommend that the report justify the current choices of studies and the use of different NOELs versus the ones used in the 1999 TAC evaluation. This is especially important in cases when NOELs chosen for the current risk assessment are higher than the NOELs used in the TAC document (see seasonal and chronic exposures).

2. Further clarification and justification is needed on absorption levels used in the RCD by inhalation and dermal routes of exposure to methyl parathion since higher values are presented in the document. However, we recommend calculating health risk values using 100 percent absorption factors for all routes of exposures.

3. We suggest presenting more than one estimate of risk (expressed as MOE) for the same exposure scenario (e.g. seasonal) in cases where the quality of the available studies justifies it. This approach was used in evaluating methyl parathion as a TAC.

4. A special section on sensitive subpopulations would improve the draft document. This section could discuss not only infants and children as potentially vulnerable groups but as also older people, people with compromised health conditions and decreased detoxification capabilities because of polymorphism of serum paraoxonase in humans.

5. We recommend that MOE calculations for children and infants apply an additional uncertainty factor of 10 to reflect pre- and post-natal sensitivities as recognized in the RCD.

6. We recommend that the discussion on the "weight of evidence" for carcinogenic potential of methyl parathion be given more emphasis on the statistically significant tumor findings, determination of whether better quality bioassays are needed, and discussion of structure-activity relationship (SAR). Based upon the information presented in the RCD, there is considerable uncertainty as to whether methyl parathion has been adequately tested for carcinogenicity.

7. A copy of the Summary of Toxicology Data for methyl parathion is not included in the packet submitted for our review. Such summaries prepared by the Medical Toxicology Branch are very informative and helpful in facilitating our review of the RCDs. We suggest that they be a part of the RCD review submission packets. We assume that there are no data gaps for methyl parathion as there was no such indication in the RCD. Usually this information can be found in the toxicology summary as noted above. A statement regarding whether data gaps exist on methyl parathion in the RCD would be helpful.

Overall we are very concerned about potential health hazards of methyl parathion that result from the acute and subchronic exposures and current non-health protective tolerances as recognized in the draft RCD. The real life hazards and resulting health risks are likely to be even higher because the risk estimates presented in the RCD do not account for pre- and post-natal toxicity, cumulative effect of other organophosphates, and potential carcinogenicity for which there is some evidence for carcinogenicity**.** Furthermore, the MOEs will be substantially reduced after the more appropriate absorption factor of 100 percent for all routes of exposure is applied.

Thank you for providing the document for our review. If you have any questions about our comments, please contact me at (510) 622-3165 or Mr. Robert Schlag at (916) 323-2624

Attachment

See next page for cc's

cc: Val F. Siebal
Chief Deputy Director
Office of Environmental Health Hazard Assessment

George V. Alexeeff, Ph.D., D.A.B.T.
Deputy Director for Scientific Affairs
Office of Environmental Health Hazard Assessment

Robert Schlag, M.Sc., Chief
Pesticide Epidemiology Unit
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment

Jolanta Bankowska, Ph.D.
Pesticide and Food Toxicology Unit
Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment

ATTACHMENT

COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR METHYL PARATHION

BACKGROUND INFORMATION

O, O-dimethyl O-(4-nitro-phenyl) phosphorothioate (methyl parathion) is currently registered in California as an insecticide to control insect pests on food and feed crops, that is the 13 following commodities: barley, dry beans, corn, cotton, oats, onions, dry peas, pecans, potatoes, rice soybeans, walnuts and wheat. Over 90% of its total use in California is on walnuts. Methyl parathion is one of the oldest and most toxic anticholinesterase insecticides classified as a Category I toxicant and a restricted-use pesticide. Methyl parathion is also listed under the California Toxic Air Contaminant (TAC). Identification and Control Act of 1983 (AB1807) as a chemical known to the State of California to be a Toxic Air Contaminant. Department of Pesticide Regulation (DPR) issued a report on "Evaluation of Methyl Parathion as a Toxic Air Contaminant" in August 1999. Methyl parathion is not listed under Proposition 65 as a substance known to the state to cause cancer or reproductive toxicity.

As part of our review of the draft DPR's Methyl Parathion Risk Characterization Document (RCD) we also revisited its previous risk assessment of methyl parathion as a toxic air contaminant. Our comments presented below are focused on issues of concern and do not discuss matters on which we are in agreement.

GENERAL COMMENTS

Selection of critical studies and endpoints for risk assessment in RCD

Acute Toxicity The acute NOEL of 0.025 mg/kg/day was chosen to calculate the margin of exposure (MOS) for acute exposures to methyl parathion by all routes (Minnema, 1994a). This NOEL was based on severe cholinesterase (ChE) inhibition (plasma, R BC and brain), clinical signs of cholinergic toxicity, peripheral nerve demyelination at the LOEL of 7.5 mg/kg/day and some indication of demyelination at the NOEL.

Subchronic Oral Toxicity The estimated NOEL of 0.03 mg/kg/day was used to calculate the MOE for subchronic (seasonal) exposures. This NOEL was derived from a developmental neurotoxicity study in rats, which showed a reduction in the ChE activities in the plasma, RBC and brain at a LOEL of 0.03 mg/kg/day (Beyrouty, 2002). The same NOEL was also used to calculate seasonal inhalation MOEs.

Subchronic Dermal Toxicity The estimated (ENEL) NOEL of 0.03 mg/kg/day was applied to calculate the MOE for subchronic (two-months seasonal) exposures. This ENEL was derived from a four-week dermal neurotoxicity study in rats. It was based on the inhibition of the ChE activities in the brain and in the RBC, and cholinergic toxicity at a LOEL of 0.03 mg/kg/day (Beyrouty, 2001).

Chronic Toxicity A NOEL of 0.02 mg/kg/day, estimated from a LOEL of 0.2 mg/kg/day in mice showing 19 percent of brain ChE inhibition in a two-year oral study in mice was used to calculate the dietary chronic exposure to methyl parathion (Eiben, 1991).

Critical studies and endpoints for risk assessment in the TAC document

Acute Toxicity There were two NOELs used to calculate the MOEs. One was the same as the NOEL used in RCD (0.025 mg/kg/day) and the other one was of 0.31 mg/kg/day (Rider *et al.*, 1970, 1971). The latter was based on 23 percent inhibition of plasma ChE and 55 percent inhibition of RBC ChE which occurred at the LOEL of 0.34 mg/kg/day after 30 days of oral dosing in human study.

Subchronic Toxicity There were four NOELs used to calculate the MOEs for the nine-month seasonal exposures. Three of them are lower than the NOEL of 0.03 mg/kg/day selected in the current RCD. These NOELs can be characterized as follows:

1. An estimated NOEL of 0.003 mg/kg/day based on a LOEL of 0.03 mg/kg/day in dogs showing 19 percent ChE inhibition (Daly, 1989).
2. A NOEL of 0.029 mg/kg/day based on 28 percent RBC ChE inhibition at the LOEL of 0.29 mg/kg/day (Minnema, 1994b).
3. An estimated NOEL of 0.02 mg/kg/day based on a LOEL of 0.2 mg/kg/day in young rats showing > 24 percent ChE inhibition in five regions of brain (Kumar and Desiraju, 1992), as well as a LOEL of 0.22-0.44 mg/kg/day showing neurobehavioral effects (Schultz *et al.*, 1990).

The fourth NOEL used to calculate the MOE for the nine-month seasonal exposures was a human NOEL of 0.31 mg/kg/day (Rider *et al.*, 1970, 1971) based on 24 percent inhibition of plasma ChE and 55 percent inhibition of RBC ChE that occurred at the LOEL of 0.34 mg/kg/day after 30 days of oral dosing.

Chronic Toxicity There were two NOELs used to calculate the MOEs. One was the same as in the RCD (0.02 mg/kg/day) and the other was lower. It was an estimated NOEL of 0.01 mg/kg/day based on a LOEL of 0.09 mg/kg/day in rats showing 17 percent RBC ChE inhibition (Bomhard *et al.*, 1981).

We suggest that DPR consider comparing choices of NOELs and critical studies used for methyl parathion risk assessment in the current (RCD) and previous (TAC) document. This is especially important in cases when NOELs chosen for current risk assessment are higher than the NOELs used in TAC document (see seasonal and chronic exposures). Choices made in the RCD should be substantiated. Another way to approach this situation would be to calculate and present sets of MOEs based on different NOELs (derived from good quality studies). This would give risk managers a broader view on risks resulting from different exposure scenarios and may be helpful in making decisions on mitigation measures.

Absorption levels of methyl parathion by different routes of exposure

Exposure estimates and MOEs were calculated in the RCD by using 100 percent oral, 50 percent inhalation and 14 percent dermal absorption.

Based on the available data on pharmacokinetics and toxicity dose-response relationship (see pgs. 25-32 of the main document), the estimated absorption for oral and inhalation routes was 100 percent (Reed, 1999). According to recent scientific reports dermal absorption for methyl parathion was also nearly complete (100%, Abu-Quare and Abu-Donia 2000 and Abu-Quare *et al.*, 2000; Sved, 2001).

Both inhalation and dermal absorption levels used by the WH&S branch to determine the occupational exposures do not seem to be appropriate. We recommend that 100 percent absorption be used to determine exposure levels by all routes of exposure. It is worthwhile to note that the currently presented occupational MOEs, which are not considered health protective using DPR criteria, will even be lower.

Groups especially sensitive to methyl parathion exposures

Pre- and post-natal sensitivity is comprehensively presented and discussed in different parts of the RCD (Toxicology Profile pgs 88-112, Issues Related to the Food and Quality Protection Act pgs 178-179).

The toxicological data for methyl parathion in rats showed that neonates can be up to 10-fold more sensitive than adults (III B. 3.). Higher sensitivity was indicated in various toxicological studies. In rats, fetal toxicities including ossification, survival, body weight and reduced brain ChE activities occurred at the same doses as the maternal toxicity (maternal weight gain, survival, reduced brain ChE activities; (Gupta *et al.*, 1985, Becker *et al.*, 1987). In a rabbit teratology study, methyl parathion doses which caused thickened areas of rib ossification in fetuses had no effects on the dams (Hoberman, 1991). In the two reproductive toxicity studies,

a reduction of pup survival was observed on day four (Daly and Hogan, 1982) and up to week four (Loser and Eiben, 1982) after birth. In the first study, the reduction of maternal body weight gain and pup survival occurred at the same doses of methyl parathion (Daly and Hogan, 1982), whereas in the second study the decreased pup survival occurred in the absence of maternal toxicity (Loser and Eiben, 1982). Recently published developmental neurotoxicity study showed that exposure to methyl parathion affected the neural development (Beyrouty, 2002). In this study immature rats repeatedly exposed to methyl parathion showed two to three-fold higher ChE inhibition in the RBC and brain than the adults. OEHHA suggests that an additional 10-fold factor be used for the interpolation of the MOE for methyl parathion exposure due to the unique sensitivities and susceptibility of infants and children.

No other possibly more sensitive group of human population is mentioned or discussed in the document. We suggest that DPR mention older people as a group especially vulnerable to methyl parathion exposures because of their diminished capacity (organ function and compensatory reserves) to detoxify and eliminate chemical toxicants. People with compromised health conditions and decreased detoxification capabilities because of polymorphism of serum paraoxonase could also be discussed. A special section on sensitive subpopulations would benefit the RCD.

Potential oncogenic effects

Methyl parathion was genotoxic in most of the available *in vitro* and *in vivo* tests. It caused gene mutations in bacteria, chromosomal aberrations in mammalian cells, sister chromatid exchange (SCE); and was positive on the sex-linked recessive lethal assay in *Drosophila. In vitro* methyl parathion was shown to bind directly to the cellular DNA.

In spite of strong evidence for genotoxicity and direct binding to cellular DNA *in vitro*, the available bioassays in rodents were evaluated as not showing clear evidence of methyl parathion oncogenic potential. "Clear evidence" would have been provided if the incidence of various kinds of tumors observed in the available studies were statistically significant.

The relevant studies discussed in details in the RCD (pg 69-76) include: two-year study with Wistar rats by Bombard *et al.*, (1981), the lifetime study by Daly and Hogan in Spraque-Dawley CD rats (1983), 105-week feeding study in F344 rats (NCI, 1979) and two studies conducted in B6C3F1 mice, one by Eiben (1991) and the other by the National Cancer Institute (NCI, 1979).

In the study by Bombard *et al.*, (1981) various types of tumors were found in 15 organ/tissue sites. Tumors with higher occurrence levels (at least 10 percent in any dose group) were found in the adrenal medulla, the uterus and pituitary, thyroid, and mammary gland. Some of these tumors, e.g,. uterus adenocarcinomas, exceeded the historical range of incidences even though the incidence levels (mid and high dose groups) were not statistically significantly different from the concurrent controls. In the study by Daly and Hogan (1983), tumors occurred

mainly in the adrenal cortex, thyroid follicular cells, mammary glands and uterus endometrial. Again, even though at the two highest dose level groups the incidence of adenocarcinomas in uterus endometrial exceeded the range of historical incidence, these incidences were not statistically different when compared with the concurrent control groups. The same applies to the third study in rats (NCI, 1979). The incidence rate of tumors such as adrenal cortex adenomas, adrenal pheochromocytomas, thyroid follicular cell carcinomas, thyroid C-cell adenoma/carcinomas and mammary gland fibroadenomas was not statistically significant when compared with concurrent control groups.

Oral studies conducted in B6C3F1 mice did not reveal any statistically significant increases in tumor incidence. In the study by Eiben (1991) some but not statistically significant increase in tumor incidence was shown for the lung bronchiolo-alveolar tumors. Exactly the same conclusion for the same type of tumors was drawn from the study in B6C3F1 mice performed by the National Cancer Institute (NCI, 1979).

Besides the above studies designed to test potential oncogenic effects, tumors (adrenal cortex adenomas and endometrial adenocarcinomas) were found in a two-generation reproductive toxicity study (Daly and Hogan, 1982). No conclusion about the significance of these results was made in the RCD (see page 72-73).

Overall we acknowledge the comprehensive, broad discussion on the potential oncogenic effects of methyl parathion. However, in our opinion the issue needs further consideration. It seems that the currently available data do not support the view that methyl parathion has no oncogenic potential for humans. We admit that the available bioassays did not show “clear evidence” of oncogenic potential but they still show some degree of evidence. We suggest that the RCD provide more discussion on statistically significant increased tumor findings in the long-term toxicity studies, weaknesses of these studies, and whether a new bioassay could be useful. We also suggest that structure-activity relationship (SAR) be included as an important part of discussing the oncogenic potential of methyl parathion.

Adequacy of testing for carcinogenic potential

Methyl parathion has been tested in three sets of bioassays in the rat (Bomhard et al, 1981; Daly and Hogan, 1983; NCI, 1979), and two sets of bioassays in the mouse (NCI, 1979; Eiben, 1991). Based on the descriptions of the studies provided in the RCD, it is unclear whether methyl parathion was tested adequately, or at sufficiently high doses (i.e., a minimally toxic dose (MTD)) in these studies to provide the maximum ability to detect treatment-related carcinogenic effects, while not compromising the outcome through excessive toxicity.

For example, in Bomhard et al. (1981) Wistar rats received 0, 2, 10 and 50 ppm methyl parathion in the diet for two years. Tumor findings included a statistically significant ($p<0.05$) increase in thyroid adenomas in high-dose males, and an increase in uterus adenocarcinoma in treated females. An elevated thyroid adenoma/adenocarcinoma incidence in male rats fed 50 ppm of methyl parathion (12/47 animals compared to 5/49 for controls) was statistically significant as determined by the Fisher exact test ($p = 0.044$). Additionally, analysis of the data set using ToxRisk indicates that a trend test for dose-response would also be significant ($p = 0.005$). This indicates that the description of the Bomhard et al. (1981) male rat thyroid adenoma data in the RCD as being marginally statistically significant is unjustified; these data unambiguously indicate that 50 ppm methyl parathion produces an increase in thyroid adenomas/adenocarcinomas in male Wistar rats. The description of the study in the RCD should be changed to reflect this fact.

In addition, reported effects on body weight (body weights of high-dose animals of both sexes were approximately 9% lower than controls) and mortality do not suggest that the MTD was reached, nor is it clear from the discussion of other treatment-related effects (e.g., deceased plasma protein levels, increased plasma urea, increased protein in urine) whether these effects occurred to a similar or lesser extent as those seen during chronic carcinogenicity testing of other acetyl cholinesterase inhibitors. Regarding mortality, p. 62 of the RCD reports mortality at six months in high-dose females as 16% (eight out of 50 animals), however, at 12 months only one additional high-dose female had died (Table 10 of the RCD). Regarding mortality in controls, page 62 of the RCD indicates that controls consisted of 100 rats per sex, yet Table 10 indicates that only 49 control females (and 49 control males) survived past week 52. It would be helpful to present information in the RCD on survival for all groups during the second year of these studies, and on whether early deaths were attributed to methyl parathion, or other factors. Thus, it is unclear whether methyl parathion was adequately tested for carcinogenic potential in these studies by Bomhard et al. (1981).

In a second example, in the studies of Daly and Hogan (1983), rats received 0, 0.5, 5 and 50 ppm methyl parathion in the diet. These studies were limited by high rates of infection (greater than 50% of the animals in all groups had chronic interstitial pneumonia) in all groups, and by excessive early mortality (33-42% survival at two years), rendering them non-informative as to the carcinogenic potential of methyl parathion.

In a third example, in the studies of Eiben (1991), mice received 0, 1, 7, and 50 ppm methyl parathion in the diet. Reported effects of methyl parathion treatment on body weight (body weights of high-dose animals were increased by 2-10 % over controls) and mortality (mortality at 52 weeks was 0, 0, 2, and 6 %, for controls, low-, mid-, and high-dose animals, respectively; mortality at 104 weeks was 16, 0, 20 and 20% for the same groups) do not suggest that the MTD was reached, nor is it clear from the discussion of other treatment-related effects (e.g., brain cholinesterase inhibition, RBC cholinesterase inhibition) whether these effects occurred to a similar or lesser extent as those seen during chronic carcinogenicity testing of other acetyl cholinesterase inhibitors. Thus, it is unclear whether methyl parathion was adequately tested for carcinogenic potential in these studies by Eiben (1991).

Finally, in the studies of NCI (1979), mice received time-weighted average doses of 0, 35, and 77 ppm methyl parathion in the diet. No treatment-related effects on mortality were observed, and only slightly lower body weights were reported in high-dose animals, suggesting that the MTD was not reached. Again, it is unclear whether methyl parathion was adequately tested for carcinogenic potential in these NCI studies.

Summary of Toxicology Data

A copy of the summary of toxicology data for methyl parathion is not included in the packet submitted for our review. These summaries prepared by the Medical Toxicology Branch are very informative and helpful in facilitating our review of the RCDs. We suggest that they be a part of the RCD review submission packets. We assume that there are no data gaps for methyl parathion as there was no indication in the RCD. Usually this information can be found in the toxicology summary as noted above. A statement regarding whether data gaps exist on methyl parathion in the RCD would be helpful.

SPECIFIC COMMENTS

(Page 70) The characterization of a p value of less than 0.05 is claimed to be "marginally" significant statistically. This should be changed.

(Page 73) The footnote c to Table 11 appears in error; "0.5" ppm should be substituted for "5.0" ppm.

(Page 76) In discussing the number of animals in the control groups in the NCI mouse studies, replace " rats" with "mice."

(Page 90) Section III.F.3. Male and female Reproductive Toxicity in Rodents. In this section, the information on the rationale for the use of hemicastrated animals in the study by Dhondup and Kaliwal (1997) if provided by the authors will be helpful.

(Page 94) Second Paragraph. Fetal effects if any should be included for the study.

(Page 95) In the study by Kumar et al., (1996) including the incidence of fetal skeletal effects if available is recommended. If such data are not available the same information should be mentioned.

(Page 98) "…yoke" should be changed to "yolk".

(Page 181) V.E.4. Endocrine Effects. The spelling should be corrected.

Conclusion

The draft RCD for methyl parathion needs further revision. The actual health risks resulting from exposures to this chemical are likely to be higher than estimated as presented. The major issues recommended for consideration include: using 100 percent absorption level for all routes of exposures and applying an additional uncertainty factor of 10 in calculating risks for children. Other issues that are suggested to be discussed, explained or better justified would help to enhance the quality of the document.

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